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Asymmetric Reduction with Bis(NADH) Model Compounds Bridged by Tartaric Acid Derivatives

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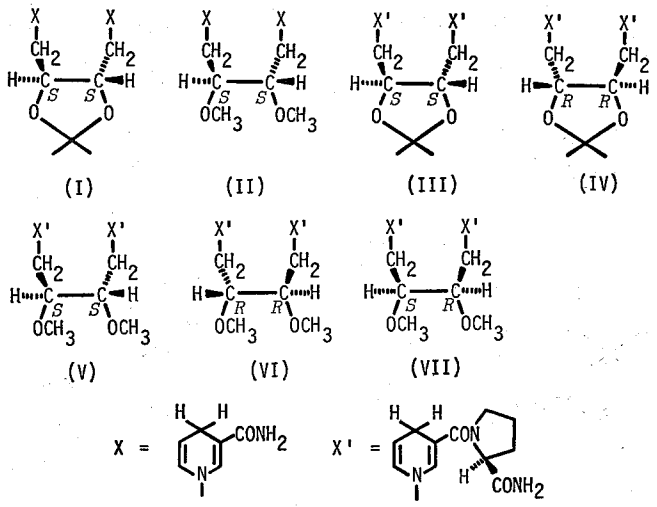
Bis (NADH) model compounds were prepared in which two achiral nicotinamide or chiral nicotinic acid derivatives of (*S*)-prolinamide were spanned with 4-carbon chains derived from (*S,S*)-, (*R,R*)- and (*R,S*)-tartaric acids. By use of these compounds, asymmetric reduction of some prochiral substrates has been carried out. It was found that the structural variations in the *N-N'* bridge were sensitively reflected in the asymmetric induction, although the product stereochemistry was determined primarily by the (*S*)-prolinamide in the 3-carbamoyl groups, and the contributions of the individual asymmetric centers were not simply additive.

KEY WORDS: NADH Model Reaction/ Asymmetric Reduction of Ethyl Benzoylformate/ Chiral Bis(NADH) Model Compounds/

INTRODUCTION

The study of asymmetric synthesis involving nonenzymatic NADH model reactions is of current interest, and a number of interesting results have been reported. In the



Scheme for structures I~VII

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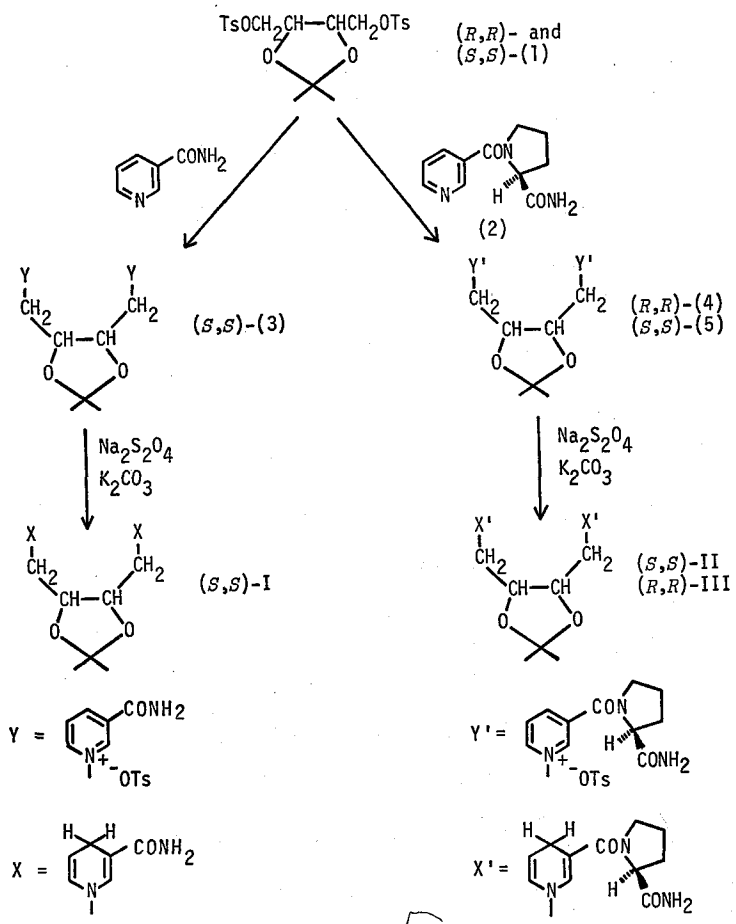
course of our study, we have found that *p*-xylylene or hexamethylene bridged bis (NADH) model compounds carrying L-prolinamides as the chiral source showed very high stereoselectivity in the asymmetric reductions of some prochiral substrates. The selectivity was explained by a hypothesis that the reaction species assumed a C_2-conformation and only the specific side hydrogens could participate in the reduction of substrates.

At present, however, little has been known about the stereochemical feature of the bis(NADH) model compounds in the asymmetric reduction of various carbonyl substrates. Thus, we designed and prepared the modified bis(NADH) mimics, **I**, **II**, **III**, **IV**, **V**, **VI** and **VII** in which two achiral nicotinamides or chiral nicotinic acid derivatives of (*S*)-prolinamides were spanned with 4-carbon chains derived from (*S*,*S*)-, (*R*,*R*)- and (*R*,*S*)-tartaric acids. These bis-reductants are characterized not only by the additional chiralities on the bridge having rigid or rather flexible structure but also by the ether oxygen functions capable of chelating with magnesium catalyst. This investigation was undertaken to gain further informations about what chirality in the molecule of the bis-reductants are important in determining the stereochemical



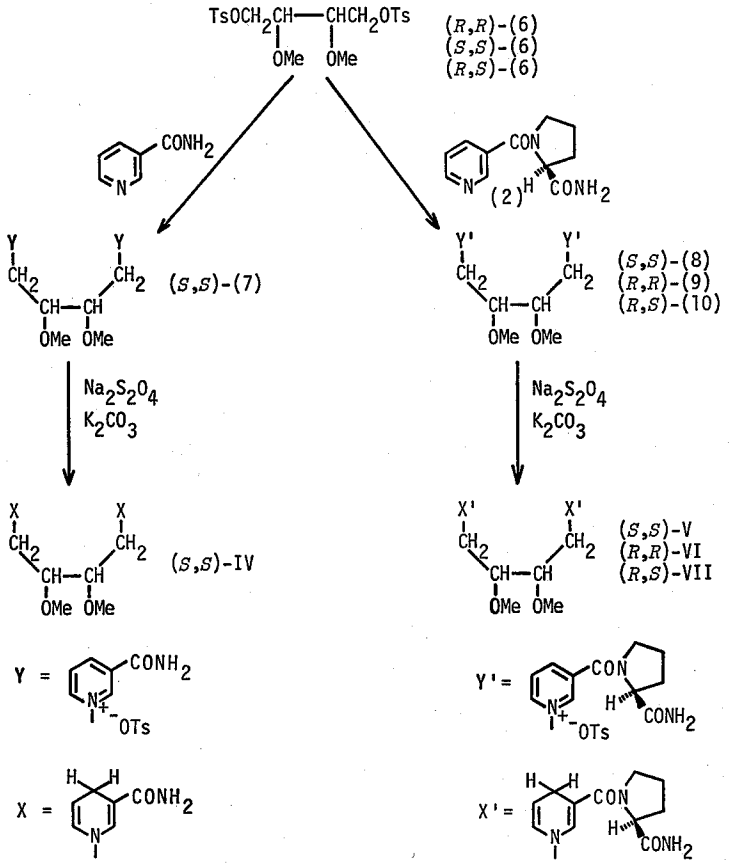
Preparation scheme 1

course of the hydrogen transfer and the stereoselectivity toward enantiotopic faces of the substrate.

RESULTS AND DISCUSSION

Preparation of bis(NADH) model compounds with (S,S)-, (R,R)- and (R,S)-tartaric acid derivatives.

Commercially available (*R,R*)- or (*S,S*)-diethyl tartrate was converted to the corresponding ditosylate (**1**) according to the method by Valentine.[3] Quaternization of (**1**) with an L-prolinamide derivative of nicotinic acid (**2**)[2f] afforded the oxidized forms (**4**) and (**5**) which were reduced to the models **II** and **III** with sodium dithionite in phosphate buffer (pH 7.1). The reductant I was prepared similarly from (*S,S*)-ditosylate (**1**). Alternatively, (*R,R*)- or (*S,S*)-diethyl tartrate was converted to dimethyl ether by the use of dimethyl sulfate with extreme care for avoiding racemization[4]. Starting from these enantiomeric esters, the models **IV**, **V**, **VI** and **VII** were prepared as described above. The integrity and purity of all the model compounds thus prepared were confirmed by NMR, UV spectroscopy, TLC analysis and polarimetry.



Preparation scheme 2

Asymmetric reduction of ethyl benzoylformate with bis-reductants

Isolated carbonyls and other unactivated substrates have not been successfully reduced as yet with the NADH model compounds under neutral and mild conditions. Among the hydrogen acceptors as activated substrate, ethyl benzoylformate was adopted in particular since a lot of information about the reduction was accumulated from both stereochemical and mechanistic aspects.

The present reductions were conducted generally in dry acetonitrile at room temperature with varying amounts of anhydrous magnesium perchlorate. Ethyl mandelate was isolated pure after usual work-up and the optical purity was polarimetrically determined. The results were graphically represented in Fig. 1 by plotting the optical yield against the amount of magnesium perchlorate. The implication of the results obtained here is not immediately clear but the following conclusion may well be deduced.

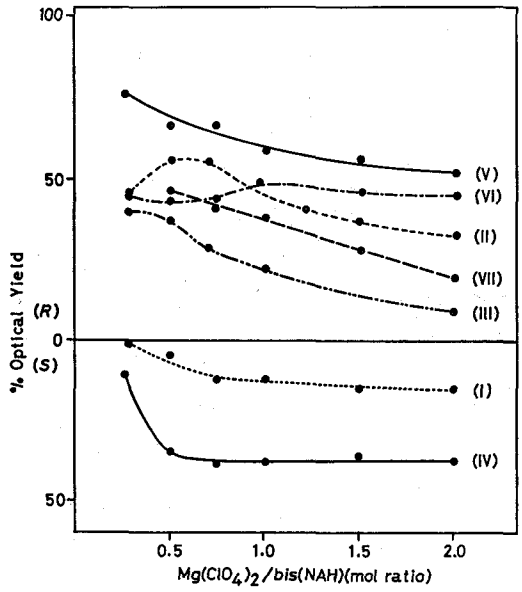


Figure 1. Dependence of the Optical Yield on the Amount of Magnesium Perchlorate.

(i) The optical yield of the product mandelate was significantly dependent on the relative concentration of $Mg(ClO_4)_2$. In the cases of the (*S,S*)-bridged reductants **I** and **IV**, the optical yields increased to about 12 and 39% respectively at the molar ratio of $Mg(ClO_4)_2$/NAH=1 and remained constant hereafter. For the reductants (*S,S*)-**III**, (*R,R*)-**V** and (*S,R*)-**VII**, the optical yields decreased monotonically by increasing the relative concentration of magnesium ion. With the model (*S,S*)-**II**, the optical yield was at a maximum (56%) with the Mg/NAH ratio of 0.5, whereas, a well bottom (40%) was observed for (*S,S*)-**VI** at the same ratio of magnesium ion concentration.

(ii) With (*S,S*)-**I** and (*S,S*)-**II** employed, ethyl (*S*)-mandelate was obtained in 1–16% e.e. with the former and 10–40% e.e. with the latter. In the case of the

bis-reductants bearing (*S*)-prolinamide derivative in addition to the chiral bridge, the enantiomeric (*R*)-mandelate was produced with (*S,S*)-**II** and (*R,R*)-**III** in 32–56% and 5–40% e.e., respectively. This shows that the chirality on the 3-carbamoyl side chain dominantly prevails over those on the bridge in producing an asymmetric bias in the reduction product. The same was also the case with models (*S,S*)-**V**, (*R,R*)-**VI** and (*R,S*)-**VII**, which gave rise to (*R*)-mandelate irrespective of the chirality on the bridge.

(iii) The comparison of the e.e. found for the chain-bridged bis-reductants **IV**, **V** and **VI** with these obtained with the ring-bridged reductants **I**, **II** and **III**, respectively, showed the former open chain-bridged reductants to be more effective than the latter ring-bridged counterparts in the asymmetric induction. This may be ascribed to the conformational adaptability of the former systems through the suitable rotation around the chain bridge to adopt the stereochemically favorable transition state conformation with the magnesium ion. In contrast, this is not the case in the latter with some conformational restrictions due to the five-membered cyclic structure.

(iv) Since the reductants (*S,S*)-**I** and (*S,S*)-**IV** gave rise to the (*S*)-mandelate in predominance, the (*R,R*)-spanned counterparts should naturally afforded the enantiomeric (*R*)-mandelate in the same optical yields, and the (*S*)-prolinamide moieties in the 3-carbamoyl side chain operated so as to favor the induction of (*R*)–chirality in preponderance. It follows that the simple additivity of asymmetric inductions due to individual chiral centers should predict that the bis(NAH) derivatives of the (*S*)-(*R,R*)-(*S*) combination will prevail over those with the (*S*)–(*S,S*)-(*S*) combination in producing the (*R*)-mandelate in excess. Contraly to the expectation, however, the comparison of the stereochemical outcome in the results obtained by use of (*S,S*)-**I** with those in (*R,R*)-**IV** and (*S,S*)-**V** with (*R,R*)-**VI** respectively, shows that the latters were found to exhibit higher stereoselectivity than the former. The implication of these experimental findings is that the simple additivity of individual contribution of chiral centers does not always hold for the multi-chiral systems and a chiral center in a given reductant does not necessarily induce the chirality in the same direction and magnitude under the quite different chiral environment of other diastereomeric molecules into which it was incorporated.

(v) One of the characteristic feature reported so far in the asymmetric reductions of ethyl benzoylformate with chiral NADH model compounds have been the dependence of the optical yield on the reaction conversion. Recently, however, it was found that some of the chiral NADH models did not show such dependence, and the complicated behaviors of the models could be related to the component ratio in the chelation complex between the model and the magnesium ion.[5] From this point of view, the same test was made with the present bis-NAH's as well. The results were shown in Fig. 2. Thus, a significant increase in optical yields was observed for **I**, **III**, **IV**, **V** and **VI** except for **II**. This outcome is in contrast to those with previously reported bis(NAH)'s in which two dihydronicotinamides with L-prolinamide are spanned by *p*-xylylene or C_6-methylene bridge, and which showed no dependence of optical yield on reaction conversion with high stereoselectivity. Accordingly, the behaviors of the present bis-systems are different from those with C_2-models described

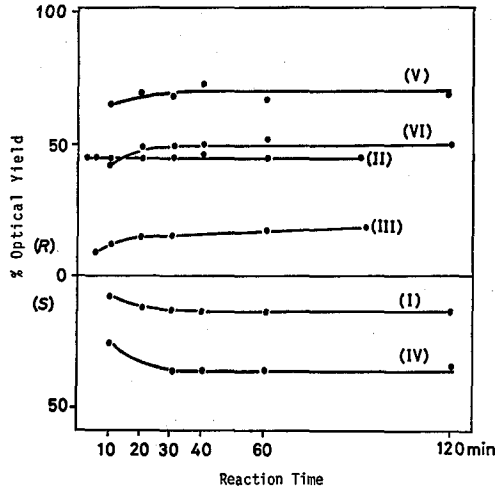


Figure 2. Dependence of Optical Yield on the Reaction Time (Reaction Conversion).

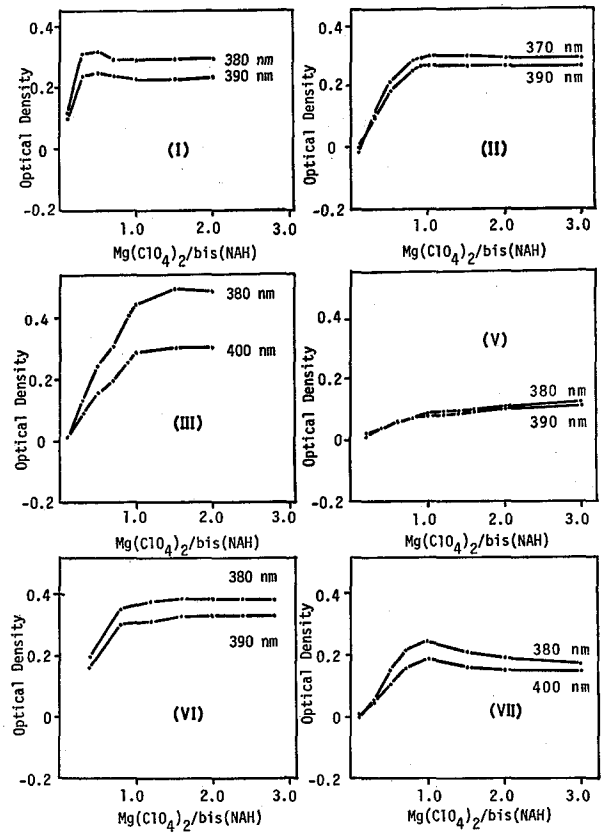


Figure 3. Chelation Properties of the Bis(NAH)'s with $Mg(ClO_4)_2$ by the Use of UV Spectroscopy.

above, and are rather similar to mono (NAH)'s reported so far[6c] which exhibit the dependence of optical yield on reaction conversion in most cases. This indicates that the present model systems bridged by chiral or achiral four-carbon chain could not take a prefered C_2-conformation requisite for high stereoselectivity, and behave like mono-NAH's.

Chelation property of the bis(NAH)'s with magnesium perchlorate

Ultraviolet absorption spectral analyses were carried out to determine the component ratio in the chelation complexes of the bis(NAH)'s with magnesium ion. The results for the reductants, **I**, **II**, **III**, **V**, **VI** and **VII** are given in Fig. 3.
An inflection point appeared at $Mg(ClO_4)_2$/bis(NAH) =1 for all the reductants except for **I** indicating formation of 1:1 or n:n (n=2, 3,.....) complexes with magnesium ions as was expected for the bifunctional bis-type model. However, the patterns are different for the models and it was ascribed to their diastereomeric relation to each other. For example, no clearcut inflection could be observed for **V**(Fig. 3) in contrast to the others. Neverthless, the model showed the highest optical yields at the magnesium ion concentrations examined here (Fig. 1). This suggests that, although the UV spectral change and the optical yield are both dependent on the metal ion concentration, the enantioselectivity can not be predicted straightforward by the mole ratio method.

On the other hand, it has been found that *p*-xylylene bridged C_2-symmetric bis (NAH)'s carrying L-prolinamide showed a maximum e.e. at $Mg(ClO_4)_2$/bis(NAH) =1 and it did not decrease with further increase in the amount of magnesium perchlorate.[2f,g] In contrast, the dependence of optical yield on amount of magnesium perchlorate was rather similar to that with mono-type models.[6b] This suggest that the present models can not assume a conformationally homogeneous C_2-symmetric complex as *p*-xylylene and C_6-methylene bridged models.

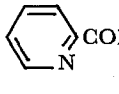
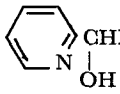
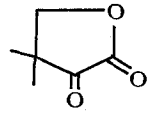
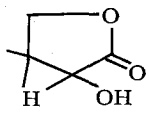
Asymmetric reduction of other prochiral substrates

Three prochiral substrates, **11–13**, were reduced to the corresponding alcohols, **14–16**, with the model **II** and the results were given in Table I. Among these, **11** and **13** afforded (*R*)-alcohols as was the case with ethyl benzoylformate. The optical yields were rather moderate comparing with the reduction of ethyl benzoylformate by use of the same models (Fig. 2). Trifluoroacetophenone afforded 2,2,2-trifluro-1-phenylethanol with (*S*)-configuration. This exceptional reversal of the product stereochemistry was also found in the asymmetric reduction with N_1-benzyl-mono (NAH)[7] and *p*-xylylene-bridged bis(NAH). However, the reason has remained obscure.

SUMMARY

So far as the present bis(NAH) system is concerned, the structural variations in the N_1-N_1' bridge, *i.e.*, chain or cyclic and the configurational reversal of the chiral centers are sensitively reflected on the asymmetric induction. The product stereochemistry is, however, determined primarily by the L-prolinamide in the 3-carbamoyl group, and the contributions of individual asymmetric centers are not simply additive. This

Table I. Asymmetric Reduction of Prochiral Substrates with Bis(NAH) (V)

Run	Substrate	Product	% Chem. yield	$[\alpha]_D^{23}$ (c, solvent)	% Optic. yield	Configuration
1	 (11)	 (14)	93.8	+32.4° (2.23, ethanol)	57.3[a]	*R*
2	$phCOCF_3$ (12)	$phCHCF_3$ (15)	11.2	+ 2.8° (1.49, benzene)	20.5[b]	*S*
3	 (13)	 (16)	40.0	−19.5° (0.96, water)	38.4[c]	*R*

a: M. Imuta and H. Ziffer, J. Org. Chem., **43**, 3530 (1978).
b: J. Jurczak, A. Konowal and Z. Krawxzyk, Synthesis, **1977**, 258.
c: E. T. Siller, S. A. Harris, J. Finkelstein, J. C. Kersztesy and K. Folkors, J. Am. Chem. Soc., **62**, 1785 (1940).

indicates that the two dihydronicotinamide moieties do not behave independently but interact with each other probably *via* intramolecular chelation control. Strong dependence of the optical yield on the metal ion concentration as well as the reacion conversion was observed in the present system too, indicating that the behavior of most of the present bis-models are similar to those with the mono-models.[8]

Finally, the present study suggests that the molecular structure including conformational flexibility of the bridge is very important in designing superior bis-type NADH model compound.

EXPERIMENTAL

General: UV, IR, ^{1}H NMR spectra were recorded on Hitachi 340, Hitachi 215, Varian EM-360 and JEOL JNM FX 100 spectrometers, respectively. The optical rotations were measured on a Perkin-Elmer 241 polarimeter. Shimadzu gas chromatograph GC-4B and GC-4CM with 5%-polyethylene glycol succinate were used for vpc analyses. Preparative vpc was performed on a Varian Aerograph Model 920. Elemental analyses were by Yanagimoto CHN Corder MT-3. Melting points were uncorrected.

General procedure for asymmetric reduction of substrates was as follows. A solution of the bis-reductant (0.81 mmol), anhydrous magnesium prechlorate (0.40 mmol) and ethyl benzoylformate (0.81 mmol) in a mixure of dry acetonitrile (33 ml) and chloroform (11 ml) was stirred at room temperature for 20 hr under nitrogen in the dark. The reaction mixture was worked up and the product ethyl mandelate was isolated as usual.[5b]

For the other prochiral substrates, a solution of the bis-reductant (1.72 mmol), anhydrous magnesium prechlorate (2.58 mmol) and substrate (1.72 mmol) in a mixture of dry acetonitrile (54 ml) and dry chloroform (18 ml) was stirred at 60°C for 30 hr under nitrogen in the dark. The isolation procedure for each product was described in our previous paper.[2g]

Preparation of ditosyl (+)-tartrate dimethylether

When methylation of hydroxyl groups of diethyl tartrate was carried out according to the method by Schmidt *et al*[4], considerable extent of racemization was observed. Accordingly, we modified the procedure as follows. Sodium hydride (2.0 g, 50% purity, 42 mmol) after washing with n-pentane was suspended in absolute diethyl ether (50 ml), to which a mixture of D-(+)-diethyl tartrate (5 g, 24 mmol) and dimethyl sulfate (6.65 g, 52.7 mmol) was added portionwise during about 30 sec under vigorous stirring and cooling with ice-water to avoid reflux. During this time, some grey solid appeared, and after the addition was completed the reaction mixture was refluxed gently for about 30 min. The reaction mixture was filtered and the cake on the funnel was washed with ether (3×100 ml). The ether was evaporated off and distillation of the residue gave the optically pure dimethyl ethers (6). Yield, 2.1 g (90%). bp. 108–110°C/2 mm. $[\alpha]_D^{22}$, +87.6° (*c* 1.045, petroleum ether). (lit.[4] bp. 90–97°C/0.7 mm, $[\alpha]_D^{20}$, +84° (*c* 1.1, petroleum ether).

General preparation of the oxidized forms

A solution of the tosylate (**1**) or (**9**) (4.36 mmol) in acetonitrile (ca. 10 ml) was mixed with an another solution of the prolinamide (**1**) in ethanol (ca. 10 ml) and the solvent was removed from the solution. The residue was heated at 135–145°C for 5 hr. The solid obtained was dissolved in a small amount of methanol. An excess of ethyl acetate was added to the solution. The liquid separated from the solution was dissolved again in a small amount of ethanol and an excess of ethyl acetate was added to the solution. Then, the residue was dried over phosphorous pentoxide under reduced pressure. All the oxidized forms presented here were extremely hygroscopic. Data of elemental analyses of these compounds were given in Table II. Their NMR

Table II. Elemental Analysis Data for the Oxidized Forms

Compound	Found (%)			Calculted for	(%)		
	C	H	N		C	H	N
(**3**)	51.53	5.74	7.24	$C_{33}H_{38}O_8N_4S_2 \cdot 4.8H_2O$	51.52	6.24	7.28
(**4**)	52.81	5.88	8.10	$C_{41}H_{50}O_8N_4S_2 \cdot 6.6H_2O$	54.18	7.00	6.16
(**5**)	52.10	6.01	8.53	$C_{41}H_{50}O_8N_4S_2 \cdot 7.7H_2O$	53.02	7.09	6.03
(**7**)	53.01	5.74	7.63	$C_{32}H_{38}O_8N_4S_2 \cdot 3.0H_2O$	53.03	6.12	7.73
(**8**)	53.40	6.07	8.61	$C_{40}H_{50}O_8N_4S_2 \cdot 5.3H_2O$	55.00	6.98	6.41
(**9**)	52.72	5.78	7.45	$C_{40}H_{50}O_8N_4S_2 \cdot 7.4H_2O$	52.71	7.16	6.15
(**10**)	53.79	6.16	7.85	$C_{40}H_{50}O_8N_4S_2 \cdot 5.7H_2O$	54.49	7.02	6.35

spectra were complicated. However, the structures of the oxidized forms were substantiated from the following characteristic signals. ^{1}H NMR (DMSO-d_6) δ (ppm from TMS): 1.3 (s, 6H, two methyl groups in isopropylidene moiety in (**3**), (**4**) and (**5**)), 2.3 (s, 6H, two methyl groups in *p*-toluenesulfonyl anions), 4.6 (4H, br, N-CH_2's in (**3**), (**4**) and (**5**)), 7.1 (4H, d, J=8 Hz, protons at β-positions to the sulfonyl groups in *p*-tolyl), 7.5 (d, J=8 Hz, protons at α-positions to the sulfonyl groups in *p*-tolyls), 8–9.7 (4H, protons on pyridinium rings).

Reduction of the oxidized forms

The sodium dithionite reduction was conducted generally as follows. To a solution of anhydrous potassium carbonate (1.27 g) and sodium dithionite (0.72 g) in water (4 ml), was added a solution of the *p*-toluene sulfonates (oxidized forms) (3.92 mmol) in water (15 ml). The mixture was stirred at 40°C under nitrogen for 2 hr. The product was extracted with chloroform four times, washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Concentration of the solution gave the model reductant as yellow oil. Their physical properties are as follows. **I**: $[\alpha]_D^{23}+7.5°$ (*c* 1.2, chloroform); UV λ_{max} (chloroform), 348 nm (ε_{max}, 7926); ^{1}H NMR ($CDCl_3$, ppm), 3.13 (4H, m, protons at 4-positions of dihydropyridines), 4.73 (2H, m, protons at 5-positions of dihydropyridines), 5.8 (2H, m, protons at 6-positions of dihydropyridines), 7.0 (2H, m, protons at 2-positions of dihydropyridines), 6.12 (4H, br, NH_2), 3.85 (2H, m, -O-CH-), 1.39 (6H, s, $-CH_3$), 3.37 (4H, m, N-CH_2). **II**: $[\alpha]_D^{22}-64.9°$ (*c* 1.23, chloroform); UV λ_{max} (chloroform), 342 nm (ε_{max}, 7854); ^{1}H NMR ($CDCl_3$, ppm), 2.05 (8H, br, protons at 3- and 4-positions of proline ring), 1.40 (6H, s, two CH_3's), 3.11 (4H, m, protons at 4-positions of dihydropyridines), 3.31 (4H, m, N-CH_2), 3.5–3.9 (6H, m, protons at 5-position of proline ring and -O-CH's), 4.4–4.8 (4H, m, protons at 5-positions of dihydropyridines and 2-positions of proline rings), 5.81 (2H, m, protons at 6-positions of dihydropyridines), 6.56 (2H, m, protons at 2-positions of dihydropyridines), 6.28 and 7.04 (4H, br, NH_2). **III**: $[\alpha]_D^{27}-68.1°$ (*c* 1.79, chloroform); UV λ_{max} (chloroform), 340 nm (ε_{max}, 7790); ^{1}H NMR ($CDCl_3$, ppm), 1.41 (6H, s, CH_3's), 2.05 (8H, br, protons at 3- and 4-positions of proline), 3.15 (4H, m, protons at 4-positions of dihydropyridines) 3.33 (4H, m, N-CH_2), 3.5–4.0 (6H, m, -O-CH- and 5-positions of proline), 4.4–4.8 (4H, m, protons at 5-positions of dihydropyridines and 2-positions of proline), 5.85 (2H, m, protons at 6-positions of dihydropyridines), 6.58 (2H, m, protons at 2-positions of dihydropyridines), 6.16 and 7.03 (4H, br, NH_2's). **IV**: $[\alpha]_D^{29}-95.3°$ (*c* 0.87, methanol); UV λ_{max} (chloroform), 345 nm (ε_{max}, 4449); ^{1}H NMRδ (DMSO-d_6, ppm), 3.00 (4H, m, protons at 4-positions of dihydropyridines), 3.25 (4H, m, N-CH_2), 3.0–3.5 (2H, m, -OCH-), 3.38 (6H, s, $-OCH_3$'s), 4.62 (2H, m, protons at 5-positions of dihydropyridines), 5.90 (2H, m, protons at 6-positions of dihydropyridines), 6.55 (4H, br, NH_2's), 6.90 (2H, m, protons at 2-positions of dihydropyridines). **VII**: $[\alpha]_D^{27}$ $-53.5°$ (*c* 1.01, chloroform); UV λ_{max} (chloroform), 341 (ε_{max}, 7990). ^{1}H NMRδ ($CDCl_3$, ppm), 2.07 (8H, br, protons at 3- and 4-positions of prolines), 3.0–3.9 (4H, m, protons at 4-positions of dihydropyridines, 2H, m, -OCH's, 4H, m, protons at 5-positions of prolines, 6H, s, OCH_3's and 4H, m, N-CH_2's), 4.5–4.8 (2H, m, protons at 5-positions of dihydropyridines and 2H, m, protons at 2-positions of prolines), 5.69, 5.81 (2H, m, protons at 6-positions of dihydropyridines), 6.51 (2H, m, protons at 6-positions of dihydropyridines), 6.05 and 6.87 (4H, br, NH_2's). **V**: $[\alpha]_D^{22}-30.6°$ (*c* 0.5, ethanol); UV λ_{max} (chloroform), 345 nm (ε_{max}, 5190); ^{1}H NMRδ (DMSO-d_6, ppm), 2.83 (8H, br, protons at 3- and 4-positions of prolines), 3.1–3.7 (2H, m, -OCH's, 4H, m, protons at 5-positions of proline, 6H, s, $-OCH_3$'s and 4H, m, N-CH_2's), 3.96 (4H, m, protons at 4-positions of dihydropyridines), 4.2–4.6 (2H, m, protons at 5-positions of dihydropyridines and 2H, m, 2-positions of prolines), 5.78

and 5.92 (2H, m, protons at 6-positions of dihydropyridines), 6.57 (2H, m, protons at 2-positions of dihydropyridines), 6.83 and 7.16 (4H, br, NH_2's). **VI**: $[\alpha]_D^{26}+63.1$ (*c* 1.0, ethanol), UV λ_{max} (chloroform), 340 nm (ε_{max}, 7305); ^{1}H NMRδ (DMSO-d_6, ppm), 2.05 (8H, br, protons at 3- and 4-positions of prolines), 2.9–3.9 (4H, m, protons at 4-positions of dihydropyridines, 2H, m, -OCH-'s, 4H, m, protons at 5-positions of dihydropyridines, 6H, s, OCH_3's and 4H, m, N-CH_2's), 4.4–4.8 (2H, m, protons at 5-positions of dihydropyridines and 2H, m, protons at 2-positions of prolines), 5.7 and 5.85 (2H, m, protons at 6-positions of dihydropyridines), 6.55 (2H, m, protons at 2-positions of dihydropyridines), 6.38 and 6.92 (4H, br, NH_2's).

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